Dkt. 45704-GA/JPW/BJA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Wai C. Wong, et al.

Serial No.: Not Yet Known

Filed: Herewith

For: DIHYDROPYRIMIDINES AND USES THEREOF

1185 Avenue of the Americas
New York, New York 10036
May 15, 2001

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT AND INFORMATION DISCLOSURE STATEMENT

Applicants request that the following amendments be made to the above-identified application:

In the Specification:

On page 1, line 2, please insert the following paragraph after the title of the invention:

> -- This application is a continuation of U.S. Serial No. 08/858,017, filed May 16, 1997, which claims priority of U.S. Provisional Application No. 60/017,801, filed May 16, 1996, the contents of both of which are hereby incorporated by reference into the subject application. --

In the Claims:

Please cancel claims 1 to 12, 24, 26, 32 to 40, 43, 44, and 46 to

52 without prejudice to applicants' right to pursue the subject matter of these claims in a future continuation or divisional application.

Please amend claims 20, 28, 41 and 45 as follows:

--20. (Amended) A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 13 and a pharmaceutically acceptable carrier.--

--28. (Amended) A method of treating a subject suffering from benign prostatic hyperplasia which comprises administering to the subject an amount of the compound of claim 13 effective to treat benign prostatic hyperplasia.--

--41. (Amended) A method of treating a subject suffering from benign prostatic hyperplasia which comprises administering to the subject an amount of the compound of claim 13 in combination with a 5 alpha-reductase inhibitor effective to treat benign prostatic hyperplasia.--

--45. (Amended) A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 13 in combination with a therapeutically effective amount of finasteride and a pharmaceutically acceptable carrier.--

Applicants attach hereto as **Exhibit 1** a Marked-up version of the

amended claims.

REMARKS

Claims 1 to 52 were pending in the subject application. By this Amendment, applicants have canceled claims 1 to 12, 24, 26, 32 to 40, 43, 44, and 46 to 52 without prejudice or disclaimer and amended claims 20, 28, 41 and 45. Accordingly, upon entry of this Amendment, claims 13 to 23, 25, 27 to 31, 41, 42 and 45 as amended will be pending and under examination.

By this Amendment, applicants have amended the specification to update the continuing data and amended claims 20, 28, 41 and 45. Support for claim 20 may be found *inter alia* in the specification, as originally-filed, at page 59, line 35 through page 60, line 1. Support for claim 28 may be found *inter alia* in the specification, as originally-filed, at page 60, lines 26 to 31. Support for claim 41 may be found *inter alia* in the specification, as originally-filed, at page 62, lines 1 to 6. Support for claim 45 may be found *inter alia* in the specification, as originally-filed, at page 62, lines 18 to 22. Accordingly, applicants maintain that this amendment raises no issue of new matter and respectfully requests that this amendment be entered.

Information Disclosure Statement

In accordance with the duty of disclosure under 37 C.F.R. §1.56 and §1.97 (a)-(b), applicants would like to direct the Examiner's attention to the following references which are listed on the attached Form PTO-1449 (**Exhibit 2**). The following references were

previously cited in connection with the prosecution of U.S. Serial Number 08/858,017 from which the subject application claims benefit under 35 U.S.C. §120. According to 37 C.F.R. §1.98(d), copies of patents or publications that were previously cited by, or submitted to, the Office in connection with such prior applications need not accompany the Information Disclosure Statement. Accordingly, copies of the following references are not attached to this Information Disclosure Statement:

1. U.S. Patent No. 4,438,117, issued March 20, 1984, Cherkofsky;

2. U.S. Patent No. 4,684,653 issued August 4, 1987 Taylor et al.;

3. U.S. Patent No. 4,684,655 issued August 4, 1987 Atwal et al.;

4. U.S. Patent No. 4,684,656, issued August 4, 1987, Atwal, et al.;

5. U.S. Patent No. 4,703,120, issued October 27, 1987, Press, J.B.;

6. U.S. Patent No. 4,728,652 issued March 1, 1988, Atwal;

7. U.S. Patent No. 4,845,216 issued July 4, 1989, Taylor et al.;

8. U.S. Patent No. 4,855,301 issued August 8, 1989, Atwal et al.;

9. U.S. Patent No. 4,882,334 issued November 21 1989, Shih et al.;

10. U.S. Patent No. 4,902,796 issued February 20, 1990 Taylor et al.;

11. U.S. Patent No. 4,946,846 issued August 9, 1990 Nomura et al.;

12. U.S. Patent No. 5,134,145 issued July 28, 1992, Brouwer et al.;

13. U.S. Patent No. 5,149,810, issued September 22, 1992, Perrior, et al.;

14. U.S. Patent No. 5,202,330 issued April 13, 1993, Atwal et al.;

15. U.S. Patent No. 5,250,531, issued October 5, 1993, Cooper;

16. U.S. Patent No. 5,292,740, issued Match 8, 1994, Burri et al.;

17. U.S. Patent No. 5,521,189, issued May 28, 1996, Boykin e al.;

18. U.S. Patent No. 5,541,186, issued July 30, 1996, Breu et al.;

19. U.S. Patent No. 5,500,424, issued 3/19/1996, Nagamine et al.;

20. U.S. Patent No. 5,594, 141, issued January 14, 1997, Yuan et al.;

21. U.S. Patent No. 5,942,517, issued August 24, 1999, Nagaratham et al;

22. PCT International Application No. WO 99/48530 published

September 30, 1999;

23. PCT International Application No. WO 99/07695 published February 18, 1999;

24. PCT International Application No. WO 98/51311 published November 19, 1998;

25. PCT International Application No. WO 97/42956 November 20, 1997;

26. PCT International Application No. WO 94/22829 published October 13, 1994;

27. PCT International Application No. WO 94/10989, published May 26, 1994;

28. PCT International Application No. WO 92/14453 September 3, 1992;;

29. PCT International Application No. WO 92/00741, published January 23, 1992;

30. European Patent Application No. EP 0 627 427, published December 7, 1994;

31. European Patent Application No. EP 0 622 369, published November 2, 1994;

32. European Patent Application No. EP 0 622 366, published November 2, 1994;

33. European Patent Application No. EP O 459 666, December 4, 1991;

34. European Patent Application No. EP O 400 665, published December 5, 1990;

35. European Patent Application No. EP 0 280 227, published August 31, 1988;

36. European Patent Application No. EP O 237,347, September 16, 1987;

37. European Patent Application No. EP O 236 902, published September 16, 1987;

38. European Patent Application No. EP O 234 830, published September 2, 1987;

39. European Patent Application No. EP 0 204 317, December 10, 1986;

40. European Patent Application No. EP 0 162 208, published November 27, 1985;

41. French Patent Application No. 2 610 625 A, published August 12, 1988;

42. Japanese Patent no 56.59778 5/23/81;

43. Japanese KOKAI 62-265271 11/18/87;

44. Japanese KOKAI 62-87574 4/22/87:

45. Japanese KOKAI 61-282367 12/12/86;

46. Atwal, K.S. et al., "Dihydropyrimidine Calcium Channel Blockers. 2. 3-Substituted-4-aryl-1,4-dihydro-6-methyl -5-pyrimidinecarboxylic Acid Esters as Potent Mimics of Dihydropyridines," Journal of Medicinal Chemistry (1990), 33(9): 2629-2635;

47. Atwal, K.S. et al., "Dihydropyrimidine Calcium Channel Blockers. 3. 3-Carbamoyl -4-aryl-1,2,3,4-tetrahydro-6-methyl -5-pyrimidenecarboxylic Acid Esters as Orally Effective Antihypertensive Agents," Journal of Medicinal Chemistry (1991) 34(2): 806-811;

48. Atwal, K.S. et al., "Dihydropyrimidine Calcium Channel Blockers. 2. 3-Substituted-4-aryl-1,4-dihydro-6-methyl-5-pyrimidinecarboxylic Acid Esters as Potent Mimics of Dihydropyridines," Journal of Medicinal Chemistry (1990) 33(5): 1510-1515;

49. Atwal, K.S. et al., "Substituted 1, 4-Dihydropyrimidines. 3. Synthesis of Selectively Functionalized 2-Hetero-1,4-dihyropyrimidines," Journal of Organic Chemistry (1989), 54, 5898- 5907;

50. Atwal, K.S. et al., "Synthesis of Substituted 1, 2, 3, 4-Tetrahydro-6-Methyl-2-Thioxo-50Pyrimidinecarboxylic Acid

Esters," Heterocycles (1989) 26(5): 1189- 1192;

51. Barrio, et al., "A Direct Method For Preparation of 2-Hydroxyethoxymethyl Derivatives of Guanine, Adenine, and Cytosine," Journal of Medicinal Chemistry (1980) 23(5): 572-574;

52. Boer, R., et al., "(+)-Niguldipine binds with very high affinity to Ca2+ channels and to a subtype of 1-adrenoceptors," European Journal of Pharmacology - Molecular Pharmacology Section (1989) 172: 131-145;

53. Brown, et al., "Inhibitors of *Bacillus subtilis* DNA Polymerase III. 6-(Arylalkylamino)uracils and 6-Anilinouracils," Journal of Medicinal Chemistry (1977) 20(9): 1186-1189;

54. Cho H., Takeuchi Y., Ueda M., and Mizuno A. Regioselective synthesis of N-substituted dihydropyrimidine-2(1-H) or (3H)-One. Tetrahedron Letters, Vol. 29 (42): 5405-5408, 1988;

55. Cho, H. et al., "Dihydropyrimidines: Novel Calcium Antagonists with Potent and Long-Lasting Vasodilative and Antihyperensive Activity,"Journal of Medicinal Chemistry (1989) 32: 2399-2406;

56. D'Eletto, R.D. and Javitt, N.B., "Effect of Doxazosin on Cholesterol Synthesis In Cell Culture," Journal of Cardiovascular Pharmacology (1989) 13, Supp. 2, S1-S4;

57. Forray, et. al., "The 1-Adrenergic Receptor That Mediates Smooth Muscle Contraction in Human Prostate Has the Pharmacological Properties of the Cloned Human 1c Subtype," Molecular Pharmacology(1994) 45: 703-708;

58. Khanina, E.L. et al., Alkylation of derivatives of 2-oxo-4-phenyl-6-methyl-1,2,3,4-tetrahydropyrimidine-5-carbo xlic acid. Chemical Abstracts 89: 43319 (1978);

59. Mamaev, V.P. and Dubovenko, Z.D., Pyrimidines. XXI. 5-Substituted 2-hydroxy-4,6-diphenylpyrimidines. Chemical Abstracts 73: 77187 (1970);

60. McGrath, J.C. et al., "Alpha-Adrenoceptors: A Critical Review," Medicinal Research Reviews (1989) 9, No. 4, 407-533;

61. Rovnyak, G.C. et al., "Dihydropyrimidine Calcium Channel Blockers. 4. Basic 3-Substituted-4-aryl-1,4-dyhydropyrimidine-5-carboxylic Acid Esters," Journal of Medicinal Chemistry (1992) 35(17): 3254-3263;

62. Spiers, J.P. et al., "UK-52,046 (A Novel 1-Adrenoceptor Antagonist) and the Role of -Adrenoceptor Stimulation and Blockade on Atrioventricular Conducution,: Journal of Cardiovascular Pharmacology (1990) 16(5): 824-830;

63. Triggle, D.J., "Dihydropyrimidine Calcium Channel Blockers. 2. 3- Substituted-4-aryl-1,4-dihydro-6-methyl-5-pyrimidine carboxylic Acid Esters as Potent Mimics of Dihydropyridines," Chemtracts- Organic Chemistry (Jan./Feb. 1991) p68-72;

64. Wetzel, J.M., et al., "Discovery of 1a-Adrenergic Receptor Antagonists Based on the L-Type Ca2+ Channel Antagonist Niguldipine" Journal of Medicinal Chemistry (1995) 38(10):

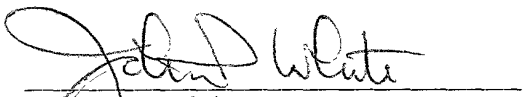
1579-1581; and

65. Zhan, G.L. et al., " Bunazosin Reduces Intraocular Pressure By Increasing Uveoscleral Outflow In Rabbits," Investigative Ophthalmology and Visual Science (1993) 34(4): Abst. No. 1133-49, p. 928.

If a telephone conference would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone the number provided below.

No fee, other than the enclosed $355.00 filing fee, is deemed necessary in connection with the filing of this Amendment and Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham LLP
1185 Ave of the Americas
New York, New York 10036
(212) 278-0400

Marked-up Version Of Amended Claims

Additions to the text are indicated by underlining; deletions are indicated by square brackets.

In the Claims

--20. (Amended) A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim [1] 13 and a pharmaceutically acceptable carrier.--

--28. (Amended) A method of treating a subject suffering from benign prostatic hyperplasia which comprises administering to the subject an amount of the compound of claim [1] 13 effective to treat benign prostatic hyperplasia.--

--41. (Amended) A method of treating a subject suffering from benign prostatic hyperplasia which comprises administering to the subject an amount of the compound of claim [1] 13 in combination with a 5 alpha-reductase inhibitor effective to treat benign prostatic hyperplasia.--

--45. (Amended) A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim [1] 13 in combination with a therapeutically effective amount of finasteride and a pharmaceutically acceptable carrier.--